REMARKS

Claims 9-15 and 17-25 are pending. Claims 17-24 were withdrawn by the Examiner.[1] However, Applicants reiterate their request rejoinder of these dependent method claims upon allowance of the product claims.

Restriction Requirement

Applicants gratefully acknowledge the Examiner's withdrawal of the restriction regarding Groups I and II.

Rejections Under 35 USC§112, ¶ 2

Applicants are grateful for the withdrawal of the rejection under 112, second paragraph.

Rejections Under 35 USC§ 103

Claims 9-15 and 25 remain rejected under 35 U.S.C. 103(a) for alleged obviousness over Lopresti et al, J. of Clinical Endocrinology and Metabolism, Vol 73, No. 4, 1992, pages 703-709 ("Lopresti") in view of Mol et al ("Mol") and Herfindal et al, In: Clinical Pharmacy and Therapeutics, 1992, pages 289-291 ("Herfindal"), and further in view of Fisher et al US 4,254,095 ("Fisher").

Furthermore, the Examiner asserts that the instant invention cannot be considered unpredictable and unexpected in view of the teaching of Bunevicius et al (Effects of Thyroxine as compared with thyroxine plus triiodothyroxine in patients with hypothyroidism, New England Journal of Medicine, 340(6):424-429 1999) "of triiodothyronine 12.5 μg/capsule administered alone" and the teaching of Miura et al (US 5,116,828, col 5, line 61 to col 6, line 49) of formulations comprising L-triiodothyronine 0.0123 mg in combination with ethinylestradiol 0.02 mg, lactose 300 mg/capsule. Applicants respectfully traverse.

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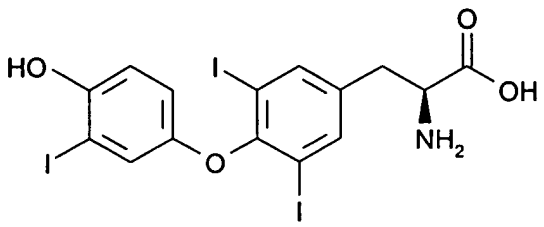
[1] Applicants note that the Office Action Summary indicates that claims 1-25 were withdrawn and that the Status of the Claims on page 2 indicates that claims 17-25 were withdrawn, but that 9-15 and 25 are under examination. Based on the finalization of the Restriction requirement and Applicants election, Applicants believe that claims 17-24 were withdrawn. To the extent the Examiner's understanding is different, please let us know.

The Cited References Do Not Teach or Suggest the Claimed Invention

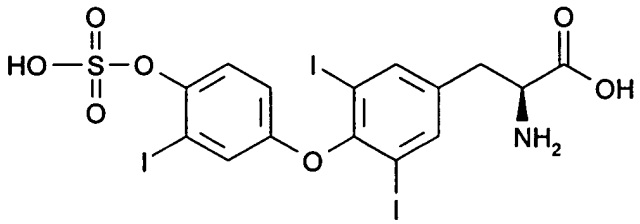
Applicants invention is directed to the oral administration of a pharmaceutical composition comprising **triiodothyronine sulfate** at the recited dose. Triiodothyronine sulfate, also known as **3,5,3'-Triiodothyronine sulfate**, and indicated by the acronym **T3S**, is a different chemical entity than the triiodothyronine (also known as T3) disclosed in the Bunevicius, Miura, and Herfindal references cited by the Examiner.

Triiodothyronine , also known as 3,5,3'-Triiodothyronine, Liothyronine, (see The Merck Index, XIII Ed. No. 5532) and indicated by the acronym **T3** is a thyroid hormone with the following structure:



As shown by at least the Bunevicius reference, T3 is known as a medicament for treatment of pathologies associated with thyroid dysfunction, but its use has significant drawbacks due to high and dangerous peaks in plasma after administration (see the clean copy of the instant specification at page 6, lines 13-15).

In contrast, Applicants have unexpectedly found that **3,5,3'-Triiodothyronine sulphate or T3S,** which is a metabolite of T3, may be administered to treat thyroid dysfunction without the drawbacks associated with T3 administration. See experimental data submitted with January 30, 2008 Amendment and Response. T3S <u>is not the sulphate salt of T3 but, rather, the conjugated sulphoric acid ester</u>), of formula:



The vast majority of the references cited by the examiner are directed to the use of **triiodothyronine (T3)** to treat thyroid or other conditions or to far less relevant subject matter.

For example, Bunevicius is directed to use of **triiodothyronine (T3)** in combination with thyroxine (T4) or T4 alone to treat patients with hypothyroidism. It neither teaches nor suggests the oral administration of T3S or the advantages associated therewith.

Miura is directed to the treatment of osteoporosis with estrogen in combination with **thyroxine (T4)** or **triiodothyronine (T3)** or pharmaceutically acceptable salts thereof.[2] It neither teaches nor suggests the oral administration of T3S for treatment of thyroid dysfunction or the advantages associated therewith.

Herfindal et al. teaches thyroid preparations including **T3** and **T4** preparations in the treatment of patients with hypothyroidism. This information and the well known drawbacks to use of T3 and T4 as thyromimetic drugs is discussed in the instant specification. (see page 5; page 6, lines 13-15 and 22-24). Herfindal neither teaches nor suggests the oral administration of T3S for treatment of thyroid dysfunction or the advantages associated therewith.

Mol et al. teaches sulfate esters of iodothyronine and their preparation and that, as the Examiner pointed out, the availability of large amounts of these compounds may facilitate the study of the importance of sulfate conjugation in the metabolism of thyroid hormones. It neither teaches nor suggests the oral administration of T3S for treatment of thyroid dysfunction or the advantages associated therewith.

Salhanic US 2002/0076827 is directed to diagnosing thyroid conditions by determining the amount of T3S in the urine. It neither teaches nor suggests the oral administration of T3S for treatment of thyroid dysfunction or the advantages associated therewith.

Fisher US 4,254,095 is directed to a radioimmunoassay for erythropoietin and does not teach or suggest compositions for treating thyroid conditions.

None of these references teaches or suggests the oral administration of **T3S** to treat thyroid conditions. Indeed, as explained in Salhanic, sulphate metabolites of T3 and T4 were known to be biologically inactive. See Salhanic, Par 0011.

Moreover, the only cited reference which actually examined administration of T3S, Lopresti, confirmed the expectation of the skilled artisan that T3S would **not** be absorbed by the GI tract given that it bears the highly polarized/ionic group $-OSO_3H$. Specifically, in order to

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[2] As T3 bears a carboxylic acid group salts thereof would include the corresponding counterions of the carboxylate group, such as sodium salts, etc. However as explained above, T3S is not a salt, but rather an ester in which the phenolic group of T3 is conjugated to sulfuric acid; thus Miura neither teaches nor suggests oral administration of T3S.

determine whether T3S is absorbed after oral administration, Lopresti administered a 1% aqueous human albumin solution of labelled T3S (see page 704, 2nd column, 3rd paragraph to the bottom) to two subjects.[3] Importantly, as a result of this study Lopresti concluded "No labelled T3S was detected in the serum of patients after oral ingestion of labelled T3S" (see page 707, 1st column); and, also: "no absorption of intact (labelled) T3S was detected after its oral ingestion" (see half of 2nd column of the abstract).

Thus, Lopresti teaches away from oral administration of T3S. One skilled in the art believing T3S exerted possible thyromimetic activity (notwithstanding the understanding in the art that it was biologically inactive) and aware of Lopresti could not have expected T3S to be properly absorbed upon oral ingestion so as to get an oral thyromimetic drug and thus would not have been induced by Lopresti to provide the novel oral compositions of the invention.

In sum, as Lopresti, the only cited reference which actually investigated the thyromimetic activity and metabolism of T3S, showed it would not be absorbed upon oral administration, the claimed compositions must be regarded as unpredictable and unexpected over the aforementioned prior art references, either taken alone or in combination. Furthermore, as none of the cited references teaches or suggests the oral administration of T3S, the dosage limitations recited in the claims cannot be deemed to be mere dose optimization.

The Claimed Compounds are Unexpectedly Advantageous Compared to the Prior Art

As explained in Applicants January 30, 2008 Amendment and Response, experimental data establishes that, contrary to the expectation of the art, T3S may be administered and absorbed by the oral route. See Experimental Data and Figures 1-5, submitted with January 30, 2008 Amendment and response. Applicants note that the copy of Fig. 5 included with their prior response was difficult to read and thus are submitting a replacement copy of Fig. 5 herewith as "Exhibit 1". In addition, because of the optimal absorption profile of T3S from the G.I. tract, administration of T3S avoids the dangerously high peaks of T3 associated with the prior art administration of T3 itself. Thus the claimed orally administered compositions and kits comprising T3S advantageously enable maintenance of steady levels of T3 in the body for

[3] Labelled T3S differs from T3S because of the presence of radioactive iodine atoms, [^{125}I], a well-known iodine isotope used for labelling purposes.

prolonged periods of time (e.g. for up to 24 hours). This is particularly advantageous in therapy where the goal is to supplement thyroid hormone in its most active form, T3, at a steady level.

Indeed, as shown in Figures 1 and 2, upon oral administration of T3S, its plasma concentration markedly increased, thus showing an unexpectedly optimal absorption profile from the G.I. tract. Plasma concentrations, in particular, were detectable shortly after the administration of T3S and the highest amounts, in plasma, were reached 4-8 hours after administration. Then, plasma concentrations of T3S slowly decreased, but were detectable 24 hours after administration. In contrast, plasma concentrations of T3S administered peritoneally peaked from 2 to 4 hours after injection (see Figure 4).

To show that plasma concentrations are dose dependent see, as per Figure 3, the results obtained at particularly high doses of oral T3S (70 μg/kg). As before, optimal absorption of T3S from the G.I tract was observed and highest plasma levels were detected 4-8 hours after administration.

These results are clearly unexpected in view of both the polar nature of T3S and the teaching in Lopresti that orally administered T3S is not absorbed from the GI tract.

Moreover, as shown in Figure 5, upon administration of TS3, the T3 concentration gradually increases and maintains a steady state level for up to 24 hours. This represents a marked improvement over administration of T3, which, as explained in the instant specification, results in potentially dangerously high peaks after administration and is rapidly cleared from the body. See e.g., specification page 5; page 6, lines 13-15 and 22-24.

Indeed, despite the clear need for therapies for deficiency of T3 (e.g. hypothyroidism), Applicants are not aware of any recent work addressed to thyroid formulations, other than instant invention, which teach or suggest the use of **oral T3S** formulations. See, e.g., Hennemann et al., Thyroid, vol. 14., No. 4, p. 271-275 (2004) (disclosing as a possible therapy for hypothyroidism slow release forms of T3 to ameliorate the unwanted non-physiologic serum peaks associated with treatment with plain (i.e., non-slow release) T3), a copy of which is attached as "Exhibit 2".

CONCLUSION

In view of the preceding remarks, it is believed that claims 9-15 and 25 are in condition for allowance. Applicants request rejoinder of claims 17-24.

If there are any questions remaining as to patentability of the pending claims, Applicants would very much desire to have a telephonic interview. The Examiner is invited to contact Applicants' undersigned attorney at the number below.

No fee is believed to be due with the filing of this Amendment. However, if any fees are deemed necessary, the Director is hereby authorized to charge such fees to Deposit Account No. 50-2168.

Favorable action is respectfully requested.

Respectfully submitted,

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